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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/991,583	SALAHUDDIN, SYED Z.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,10,11 and 13-43* is/are pending in the application.

4a) Of the above claim(s) *13-27 and 29-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10,11 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response of 24 October 2007 has been received and entered into the application file. Claims 1-5, 10, 11 and 28 have been amended; claims 6-9 and 12 have been cancelled; new claims 39-43 have been added. Claims 1-5, 10, 11 and 13-43 remain pending in the current application, of which claims 13-27 and 29-38 have been withdrawn from consideration as being directed to non-elected subject matter. Claims 1-5, 10, 11 and 39-43 have been considered on the merits.

Priority

Acknowledgement is made of applicant's claim for priority to provisional application 60/249,762, filed 17 November 2000.

Response to Arguments/Amendments

Applicants arguments received 24 October 2007 have been fully considered. The arguments, in combination with the amendments to the claims, are sufficient to overcome the rejections based on Pulford et al and Yoshioka et al, as neither of these references disclose compositions comprising *human* Kupffer cells. However, with regards to the rejection based on Gendrault et al, Applicant's arguments are not found persuasive for the following reasons:

Applicant has argued that the Gendrault et al reference is inappropriate under 35 USC 102(b), as it does not disclose each and every limitation of the instant claims. Specifically, Applicant argues that the composition of Gendrault comprises a mixed population of cells, Applicant points to Kirn et al (Hepatology, 1982), on whose isolation protocol Gendrault's method is based, to show that the composition of Gendrault would be expected to comprise 10-15% non-Kupffer cells. Furthermore,

Applicant argues that Gendrault does not show whether or not the Kupffer cells are replicating, nor does Gendrault report on the expression (or lack thereof) of CD68 and TGF-beta.

In response to Applicant's argument that Gendrault et al does not disclose each and every limitation of the instantly claimed invention, it is respectfully submitted that Gendrault et al isolated Kupffer cells in a manner substantially identical to that performed by Applicant, and reported in the instant specification. Specifically: both Gendrault et al (relying on the method of Kirn et al) and the instant application report digesting non-tumor liver biopsies from humans with a protease, centrifuging the cell suspension, recovering banded cells, plating cells on tissue culture plates in the presence of standard cell culture medium with 20% FCS, and then culturing the cells (See Kirn et al, Pg. 216; See Specification paragraphs 0044-0048). Because the cells were isolated in the same manner, from the same cell source (human liver biopsies), the resultant products (the composition comprising the Kupffer cells) are inherently the same, as well. Therefore, the Examiner submits that a factual basis has been provided for asserting the composition of Gendrault et al inherently possess Kupffer cells which have the same expression profiles as those claimed. At this point, burden is shifted to Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Furthermore, with regards to Applicant's argument that the composition of Gendrault et al is different from the instantly claimed composition because the composition of Gendrault et al comprises a mixed population of cells, it is respectfully submitted that the instant claims are directed to a composition "comprising" isolated, replicating human macrophages (see rejection under 35 USC 112, second paragraph, below), and as such, do not require the population to be free of other cells.

Applicant has also submitted several references as Exhibits 1-5, to support their position that Kupffer cells are a heterogeneous group of cells, and not all Kupffer cells express CD68, nor do all Kupffer cells replicate in vitro or in vivo. These references have each been considered, yet are not found to be sufficient to overturn the rejection of record over Gendrault et al because, as stated above, Gendrault et al obtain cells from an identical source, and perform the same isolation procedure, therefore the cells obtained by Gendrault et al inherently have the same expression profiles and replication ability as those of the instantly claimed application.

However, Applicant's point, with regards to the heterogeneous nature of Kupffer cells, is well taken. Specifically, Chedid et al (Arch Pathol Lab Med, 2004) and Naito et al (Microscopy Res & Tech, 1997) do provide evidence that not all Kupffer cells express CD68 or replicate, respectively. However, this raises the issues as to whether or not Applicant has disclosed all necessary steps to ensure isolation of Kupffer cells which do express CD68 and do replicate. Clearly if heterogeneity exists within Kupffer cell populations, further steps are necessary to ensure isolation and selection of cells with the desired characteristics. A review of the specification did not reveal any particular methods or steps to identify Kupffer cells with the specific characteristics; however, because the specification does show that at least some of the cells isolated from the liver biopsy satisfied the claim limitations, it is surmised that a liver biopsy, as obtained by the instant application method, or by the method of Gendrault et al/Kirn et al, would at least produce some cells having the desired characteristics. However, if the claims are narrowed to require clonal dilution and subsequent expansion, it must be shown that the instant disclosure is enabling for selection of cells which satisfy the claimed limitations.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 10, 11, 28 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claim 1 Applicants have added the limitation that the composition be free of Kupffer cells that do not express CD68 and that do express TGF-beta. New claims 39 and 40 require the composition of claim 1 to comprise human replicating Kupffer cells that are negative for any one or more of factor VIII R-Ag, EN-4, PAL-E, ATPase, and alkaline phosphatase, and are positive for any one or more of TPA-I, 5'nucleotidase and Ac-LDL. New claim 41 requires the composition of claim 1 to be free of non-Kupffer cells. New claim 42 requires the composition of claim 1 to be produced by clonally isolating the Kupffer cells; it is noted that clonal isolation would result in a biologically pure culture of Kupffer cells which express CD68 and do not express TGF-beta (characteristics of claim 1). These limitations are found to introduce new matter which was not supported in the disclosure as originally filed. An amendment to the claims or the addition of a new claim must be supported by the description of the invention in the application as filed. In re Wright, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989). Applicant is required to cancel the new matter in the reply to this Office Action.

A review of the specification shows that Applicant obtained liver biopsies from human patients, digested the biopsies via protease digestion, centrifuged the cell suspension, recovered the banded cells, and serially diluted them to obtain non-HCV infected cells (Paragraphs 0044-0045 of specification).

In a separate embodiment, it appears Applicant recovered the banded cells after centrifugation, washed the banded cells and plated them on gelatin in macrophage cell growth medium (MCG medium), passaged the cells, then selected and cultured eight isolates (Paragraph 0044 & 0046-0048). The morphology of the eight isolates is recorded in Tables 1 and 2. All isolates tested were reported to be

positive for non-specific esterase and acid phosphatase (Table 1), also, all isolates tested were reported to be CD68 positive, TGF-beta negative, and phagocytic (Table 2).

However, because these isolates were not clonally isolated, it cannot be assumed that all of the cell within each isolate sample are identical. There is no evidence that any one of the isolate populations were free of non-Kupffer cells or Kupffer cells that were negative for CD68. Additionally, it is noted that there is no evidence regarding the expression of any of factor VIII R-Ag, EN-4, PAL-E, ATPase, alkaline phosphatase, TPA-I, 5'nucleotidase and Ac-LDL (the specification, at the paragraph following 0048 appears to refer to Table 2 for reactivity patterns to these markers, however, this appears to be in error, as Table 2 recites reactivity to CD68, TGF-beta, and phagocytosis); therefore, it is not supported that any of the KC isolates exhibited these claimed expression profiles.

Therefore, absent a showing that clonal isolates were developed from a single cell exhibiting all of the claimed expression features/characteristics, Applicant is not deemed to be in the possession of a composition that is free of Kupffer cells that do not express CD68 (claim 1 and dependents thereof), free of non-Kupffer cells (claim 41), or Kupffer cells that express TPA-I, 5'nucleotidase and/or Ac-LDL (claim 40), or Kupffer cells that are negative for factor VIII R-Ag, EN-4, PAL-E, ATPases and/or alkaline phosphatases (claim 39).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 10, 11, 28 and 39-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 1 is directed to a composition comprising isolated human replicating Kupffer cells having a particular expression profile; the claim is considered indefinite because the preamble uses the open transitional language "comprising" (allowing for additional, non-recited elements), yet the claim recites *isolated* human replicating Kupffer cells. This is considered to be exemplary of a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation in the same claim. Such claims are considered indefinite, as they do not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). A composition of *isolated* human replicating Kupffer cells would be a biologically pure culture, yet a composition *comprising* human replicating Kupffer cells may contain other cell types (except for those specifically excluded by negative limitations). Clarification is required. For purposes of applying art, the claim is given its broadest reasonable interpretation- and will be interpreted as a composition *comprising* human replicating Kupffer cells, with the specified expression profiles.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The amended claims are interpreted as being directed to a composition comprising replicating human Kupffer cells, wherein the replicating Kupffer cells (i) express CD68 and (ii) do not express TGF-beta; but wherein the composition does not comprise Kupffer cells that do not express CD68 and that do express TGF-beta. Dependent claims require the Kupffer cells to have undergone cell division during culture *in vitro*. Dependent claims further limit the time period during which the cells must have undergone division. Other dependent claims further define the Kupffer cells as being phagocytic, staining

positive for non-specific esterase and acid-phosphatase, being negative for factor VIII R-Ag, EN-4, PAL-E, ATPase, and alkaline phosphatase expression, being positive for TPA-I, 5'nucleotidase and Ac-LDL, being non-transformed, or being from a source other than a tumor.

It is noted that the instant claims are directed to a product: a composition comprising replicating macrophages. However, claims 1-5, 10, 11 and 43 include a 'wherein clause' which states that at least some of the Kupffer cells must have previously undergone cell division during culture *in vitro*. Such 'wherein' (or 'whereby') clauses are only to be given weight when they state a condition that is material to patentability, such as imparting structural or other physical properties to the claimed product. In the instant case, requiring the cells in the composition to *have previously* undergone cell division is not interpreted as imparting any unique physiological properties to the Kupffer cells present in the claimed composition, a review of the specification also fails to point out or describe any properties or characteristics that are present in Kupffer cells after having undergone division which are not shared by a primary culture of such Kupffer cells. In fact, it the specification appears to focus on methods for maintaining Kupffer cells in culture for extended periods of time, in a manner such that the cultured Kupffer cells are *not* physiologically distinct from primary cultures, and thus may be used in transplantations and experiments which were previously limited due to time constraints. Therefore, the limitation "wherein at least some of the Kupffer cells have undergone cell division during culture *in vitro*," and the dependent limitations further defining the length of the culture period, are not considered to lend patentable weight to the product as claimed. Therefore, the product of claims 1-5, 10 and 11 is considered to read on any composition comprising replicating human Kupffer cells with the claimed expression profiles.

Similarly, it is noted that claim 28 is a product-by-process claim. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself, in the instant case: a cell composition comprising replicating human Kupffer cells. The

patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Claims 1-5, 10, 11, 28 and 39, 40 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Gendrault et al (Pathobiology, 1991).

Gendrault et al disclose viable cultures of human Kupffer cells derived from digested liver biopsies of HIV-seronegative patients being treated for liver cancer. The Kupffer cells were co-cultured with either HIV-infected CEM cells or non-infected CEM cells, in both cocultures the Kupffer cells demonstrated phagocytic properties (See Pg. 223). The Kupffer cells co-cultured with the non-infected CEM cells are considered non-transformed. Gendrault et al report successfully maintaining the Kupffer cells in co-culture with the CEM cells for at least seventeen days (See Gendrault et al, Pg. 225, col. 1); one of ordinary skill in the art would take such to mean the Kupffer cells were inherently replicating and dividing.

Though Gendrault et al do not test for or report on the expression (or lack thereof) of CD68, TGF-beta, or the ability to stain positive for non-specific esterase or acid-phosphatase, or the expression (or lack thereof) of factor VIII R-Ag, EN-4, PAL-E, ATPase, or alkaline phosphatase, these characteristics appear to be inherent to non-infected Kupffer cells isolated from liver biopsies. This assertion of inherency is based on the fact that Gendrault et al obtain the Kupffer cells the same way as performed in the instant application (See specification page 14, specifically: protease digestion of a liver biopsy, centrifuged, and the banded cells were collected, washed and plated; cells were cultured in standard culture medium + 20% FCS) and the instant application reports all cell obtained via this method (KC isolates 1-8) all shared the claimed expression profiles/characteristics (See Tables 1 and 2 of spec).

It is reiterated that merely because a characteristic of a cell culture is not disclosed in a reference does not make the claimed cell composition patentable. The known cell culture possesses inherent characteristics which might not be displayed in the tests used the reference. However, the cell culture disclosed by Gendrault et al appears to be the same as that claimed, as the cells are obtained from the same source (human liver biopsies), and isolated via the same methods (discussed above). Clear evidence that the cell culture of the cited prior art does not possess critical characteristics that are possessed by the claimed cell composition, would advance prosecution and might permit allowance of claims to applicants' composition comprising a particular cell type.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
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